REMARKS

Claims 1-29 were pending in this application. Claims 1-10, 14 and 17-29 have been cancelled without prejudice to the filing of a divisional application. Claims 11-13 and 15-16 are pending in this application, with claims 11-12 being withdrawn from consideration. Claims 13, and 15-16 are under active examination. Claims 13 and 15-16 have been amended for formal matters and to correct the antecedent basis therein.

The amendments to the claims do not constitute new matter as defined under 35 U.S.C. § 132. Applicants respectfully request entry of the amendments.

I. INTERVIEW WITH THE EXAMINER

Applicants wish to express their gratitude to the Examiner for extending an interview with the Applicants' attorney on August 7, 2003. In the interview, it was discussed that the method of determining metastasis potential of a cancer according to the invention claimed in Claims 13, and 15-16 are different from the methods suggested by the prior art of record. The distinguishing features of the invention is discussed in the present response.

II. STATUS OF THE CLAIMS

Applicants Amendment and Reply dated January 22, 2003 inadvertently stated that claims 1-12, 14, and 17-29 have been cancelled from this application. No amendment to cancel these claims, however, accompanied the Applicants' response and no amendment to the claims was filed with the USPTO. Accordingly, no claim cancellation by the way of an amendment has previously been entered in the file history of this application. Claims 11-13, and 15-16 were previously included in the elected invention of Group 4 for prosecution. The Examiner also issued an election of species requirement stating that Claims 1-3 and 11-13 are generic to several species. In the subsequent Office Action, dated Feb. 26, 2002 (Paper No. 10), the Examiner withdrew from consideration Claims 1-12, 14, and 17-29. In the present Amendment, Applicants have cancelled Claims 1-10, and 17-29 directed to non-elected invention without

prejudice for filing a divisional application. Applicants have maintained the pendency of Claims 11-13, and 15-16 in this application. Upon finding allowable subject matter in Claims 13, and 15-16, the species Claims 11-12, which are fully embraced by the allowed generic claims, would be no longer withdrawn from consideration. MPEP 809.02 (c)

III. CLAIM REJECTIONS UNDER 35 U. S. C. § 103 (a)

The Examiner rejects Claims 13, 15 and 16 under 35 U. S. C. § 103(a) as allegedly being obvious by Garcia *et al.* (1997), *Cell Growth and Differentiation* 8: 1267-1276 ("Garcia") and Takemoto *et al.* (1997), *PNAS USA* 94: 13897-13902 ("Takemoto"), further in view of University of Michigan Medical School (1997), *Prec. Ann. Meet. Assoc. Cancer Res.* 38: A375 (U. Mich. Abstract).

The Examiner has maintained the previous rejection over the cited references for the reasons of record. Specifically, the Examiner states that Garcia teaches that constitutive activation of STAT-3 protein was present in five out of nine breast carcinoma cell lines. While the Examiner notes that Garcia does not teach a method of determining the level of activated STAT-3 protein in a patient's sample as an indicator of metastasis potential of the tumor, it is the Examiner's position that Takemoto cures this deficiency by teaching that sampling STAT-3 protein can be performed in cancer patients to demonstrate cell transformation in these patients. Additionally, the Examiner maintains the rejection over U. Mich. Abstract. The Examiner contends that U. Mich. Abstract discloses high level of constitutively activated STAT-3 derived from both primary and metastatic breast tumor specimens. Applicants respectfully traverse the rejection.

Applicants respectfully submit that the references cited by the Examiner, either alone or in combination, do not teach or suggest the subject matter of the claims. Garcia, as the Examiner acknowledged, discloses that constitutive activation of STAT-3 protein was present in five out of nine breast carcinoma cell lines. Also, as the Examiner acknowledged, there is no teaching or

suggestion in Garcia that STAT-3 protein activation can be measured in a patient's sample as an indicator of the metastasis potential of the patient's cancer. Additionally, Garcia does not disclose that the activated STAT-3 protein is not mediated by JAK, or it is independent of growth hormones.

Applicants respectfully submit that Garcia does not correlate the activation of STAT-3 protein with the ability of the cells to metastasize, but rather characterizes STAT-3 protein activation as an early event in src-induced oncogenic transformation. In fact, the entire disclosure of Garcia is directed towards the role of STAT-3 protein in the transformation of cells by src or other oncoproteins. For example, Garcia, at page 1274, first column, third paragraph, states that "a critical question to ask is whether STAT is involved in the growth of normal cells or malignant cells" and further concludes that STAT is involved in oncogenic transformation of mammalian cells. Accordingly, neither the problem articulated by Garcia *et al.*, nor the solution to the problem found by Garcia *et al.*, teaches or suggests the involvement of STAT-3 protein in cancer metastasis.

It was known in the art at the time the present invention was filed that there are two prominent compartments in growing tumors: the cancer cells and the endothelial cells that make up blood vessels that feed them. The balance between the positive and negative regulators produced by the two compartments determines the ultimate growth rate and metastasis of the tumor. The results presented in the specification indicate for the first time that in addition to the role of STAT-3 protein as an indicator of cell transformation, certain activated STAT proteins may also be involved in cancer metastasis that requires the growth of blood vessels correlated with cancer, as well as, or instead of, the growth of the tumor tissue itself.

It was also well known at the time the present application was filed that tumorigenesis and metastasis could be under separate genetic control, and that the molecular mechanisms responsible for transformation of normal cells were not necessarily the same as those responsible for metastasis. See, *e.g.*, Liotta, page 145, which states that "(oncogenic transfection) models have revealed that some metastasis effector genes can be regulated independently from those that

confer tumorigenicity" For example, oncogenes such as H-Ras can induce a metastatic phenotype, but do so through pathways which differ from oncogene-induced tumorigenesis.

Takemoto discloses that activated STAT-3 mediated by JAK is found in some leukemic cells, and that JAK/STAT activation may be associated with leukemic cell proliferation. Takemoto's STAT-3 protein activation is not mediated by JAK and is not correlated with cancer metastasis. Rather, Takemoto discusses STAT-3 protein activation only in terms of cellular transformation and JAK mediation of STAT-3 activation. *See, e.g.*, page 13901, second column of Takemoto which states that "[c]onstitutive activation of JAKs and/or STATs has been correlated with cell transformation in other models of viral transformation."

With respect to the U. Mich. Abstract, Applicants respectfully submit that the Abstract discloses that STAT-3 protein is not detectable in EGF negative human breast cancer cells. In contrast, the STAT-3 protein activation of the invention occurs in tumors that grow independent of growth hormones and/or growth factors. Accordingly, STAT-3 activation of the invention is independent of EGF. Furthermore, the U. Mich. Abstract is silent on the type of kinases that would activate STAT-3 protein in metastatic tumors and does not disclose that STAT-3 protein activation not mediated by JAK is an indicator of cancer metastasis in the absence of growth hormones.

Applicants respectfully submit that, for the reasons stated above, the combination of these references, even if properly made, which is not admitted, does not teach or suggest the invention as claimed.

Accordingly, Applicant respectfully requests that the Examiner withdraw the obviousness rejection of claims 13, and 15-16.

CONCLUSION

In light of the above, Applicant respectfully submits that all pending claims are allowable over the art of record, and a Notice of Allowance is courteously solicited. The foregoing is submitted as a full and complete response to the Office Action dated April 8, 2003.

The Examiner is invited and encouraged to contact the undersigned attorney of record if such contact will facilitate an efficient examination and allowance of the application.

Respectfully submitted,

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